End of Result Set

L6: Entry 2 of 2 File: DWPI Sep 15, 1994

DERWENT-ACC-NO: 1994-302928
DERWENT-WEEK: 199601

TITLE: Use of tripterinin, a diterpene from medicinal plant sources - in autoimmune disease, e.g., arthritis, and tissue transplant rejection

Basic Abstract Text (2):
USE/ADVANTAGE - (I) reduce cytokine abnormalities, a feature of autoimmune disease, notably IL-1, IL-6, and TNF-alpha, in serum and synovial fluid. These diseases include partic. rheumatoid arthritis, also Addison's disease, allergies, asthma, atherosclerosis, Crohn's disease, type 1 diabetes, Graves' disease, Guillain-Barre syndrome, lupus erythematosis, multiple sclerosis, myasthenia gravis, psoriasis, primary biliary cirrhosis, and uveitis. (I) is also useful for treatment of transplant rejection of heart, kidney, liver, and bone marrow, and for graft rejection, including late graft rejection, and for suppression of graft vs host disease. In both cases, (I) can be used either alone, or in compsns. with cyclosporin A, azathiorpine, methotrexate, or a glucocorticoid as other immunosuppressive agent. (I) are free from the objections of protein or antibody therapy methods, with risk of immunogenicity or over-secificity. (I) is also active orally.

WEST

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Search Results - Record(s) 1 through 2 of 2 returned.

☐ 1. Document ID: WO 200137874 A2 AU 200130824 A

L7: Entry 1 of 2 File: DWPI May 31, 2001

DERWENT-ACC-NO: 2001-367621
DERWENT-WEEK: 200138
COPYRIGHT 2002 DERWENT INFORMATION LTD
TITLE: Use of anti-tumor necrosis factor alpha antagonist, in particular anti-tumor necrosis factor alpha antibody or its antigen-binding fragment for treating psoriasis or psoriatic lesions in an individual

INVENTOR: SHEALY, D J

PRIORITY-DATA: 1999US-167470P (November 24, 1999)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 200137874 A2	May 31, 2001	E	021	A61K039/395
AU 200130824 A	June 4, 2001		000	A61K039/395

INT-CL (IPC): A61 K 39/395

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

☐ 2. Document ID: WO 9420488 A1 US 5468772 A AU 9464002 A

L7: Entry 2 of 2 File: DWPI Sep 15, 1994

DERWENT-ACC-NO: 1994-302928
DERWENT-WEEK: 199601
COPYRIGHT 2002 DERWENT INFORMATION LTD
TITLE: Use of tripterinin, a diterpene from medicinal plant sources - in autoimmune disease, e.g., arthritis, and tissue transplant rejection

INVENTOR: WIEDMANN, T W; XU, R S

PRIORITY-DATA: 1993US-0031288 (March 10, 1993)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 9420488 A1	September 15, 1994		049	C07D311/00
US 5468772 A	November 21, 1995		000	A61K031/35
AU 9464002 A	September 26, 1994		000	C07D311/00

INT-CL (IPC): A61 K 31/35; A61 K 31/365; C07 D 311/00

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Clip Img | Image

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Term	Documents
TUMOR.DWPI,EPAB.	13585
TUMORS.DWPI,EPAB.	7901
TUMOUR.DWPI,EPAB.	19182
TUMOURS.DWPI,EPAB.	10193
NECROSIS.DWPI,EPAB.	4621
NECROSES.DWPI,EPAB.	65
FACTOR.DWPI,EPAB.	101916
FACTORS.DWPI,EPAB.	25323
PSORIASIS.DWPI,EPAB.	10728
PSORIASI	0
((TNF$ OR TUMOR ADJ NECROSIS ADJ FACTOR) SAME ANTIBOD$ AND (PSORIASIS OR PSORIATIC) AND METHOTREXATE).EPAB,DWPI.	2

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Search Results -

Term	Documents
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TUMORS.DWPI,EPAB.	7901
TUMOUR.DWPI,EPAB.	19182
TUMOURS.DWPI,EPAB.	10193
NECROSIS.DWPI,EPAB.	4621
NECROSES.DWPI,EPAB.	65
FACTOR.DWPI,EPAB.	101916
FACTORS.DWPI,EPAB.	25323
PSORIASIS.DWPI,EPAB.	10728
PSORIASI	0
PSORIATIC.DWPI,EPAB.	728
((TNF$ OR TUMOR ADJ NECROSIS ADJ FACTOR) SAME ANTIBOD$ AND (PSORIASIS OR PSORIATIC) AND METHOTREXATE).EPAB,DWPI.	2

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- US Pre-Grant Publication Full-Text Database
- JPO Abstracts Database
- EPO Abstracts Database
- Derwent World Patents Index
- IBM Technical Disclosure Bulletins

Search: Refine Search

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Search History

DATE: Thursday, December 05, 2002 Printable Copy Create Case

Set Name side by side	Query	Hit Count	Set Name result set
DB=EPAB,DWPI; PLUR=YES; OP=ADJ			
L7	(tnf$ or tumor adj necrosis adj factor) same antibod$ and (psoriasis or psoriatic) and methotrexate	2	L7
L6	(tnf$ or tumor adj necrosis adj factor) same antibod$ same (psoriasis or psoriatic) and methotrexate	2	L6
DB=USPT; PLUR=YES; OP=ADJ			
L5	(tnf$ or tumor adj necrosis adj factor) same antibod$ same (psoriasis or psoriatic)	110	L5
L4	(tnf$ or tumor adj necrosis adj factor) same antibod$ and (psoriasis or psoriatic)	690	L4
L3	5919452.pn.	1	L3
L2	5672347.pn.	1	L2
L1	6190691.pn.	1	L1

END OF SEARCH HISTORY

L5: Entry 38 of 110 File: USPT Feb 20, 2001

DOCUMENT-IDENTIFIER: US 6190691 B1
TITLE: Methods for treating inflammatory conditions

Brief Summary Text (7):
In chronic inflammatory conditions, elevated tissue levels of several mediators including the cytokines IL-1, IL-8, GM-CSF, and TNF have been found in the inflamed joints of patients with rheumatoid arthritis (RA) (see Yocum, et al., Cellular Immunol. 122:131-145 (1989) and Hopkins, et al., Clin. Exp. Immunol. 73:88-92 (1988)). With synovial culture systems, it was demonstrated that TNF regulated the production of GM-CSF and IL-1 in addition to expression of more TNF receptors making TNF seminal in this disease pathogenesis. Similarly, there is an increased level of TNF in the intestinal mucosa (Olson, et al., J. Pediatric Gastroenterology and Nutrition 16:241-246 (1993)) and in the feces (Nicholls, et al., J. Clin. Pathol. 46:757-760 (1993)) in patients with inflammatory bowel diseases (IBD, includes Crohn's disease and ulcerative colitis). While it is generally recognized that chronic inflammation is a complex cellular and molecular event, it has been suggested that cytokine mediators do not act in parallel, but in series. This view has been verified recently by clinical results demonstrating a clear resolution of both severe RA (Elliott, et al., Arthritis and Rheumatism 36:1681-1690 (1993)) and IBD upon administration of anti-TNF antibody. Thus, TNF is found to be the key mediator in these two diseases and, in various other inflammatory conditions including psoriasis, asthma, cancer, infection, and cachexia associated with AIDS and cancer.

Detailed Description Text (126):
The ACD reaction is marked by an influx of lymphocytes and monocytes into the affected area and is characterized by distinctive swelling, redness, and itching. In contrast to dermatologic diseases such as psoriasis where the etiology is poorly understood, the immunological basis of ACD is known in detail, and the reaction which occurs in humans can be accurately reproduced in various animals. Several elegant studies have clearly demonstrated the critical roles of both IL-1 and TNF in ACD. These experiments have shown that IL-1.beta. is a critical mediator in the sensitization phase of allergic contact dermatitis (neutralization of IL-1.beta. prevents sensitization to various allergens). However, it has been shown recently that epidermal TNF production is critical to Langerhans cell migration to the local lymph nodes where antigen presentation to T-cells takes place during the sensitization phase of ACD. Within 2-24 hours following poison ivy exposure (i.e. ACD), rapid onset of epidermal TNF protein expression was observed with a slower onset of IL-8 expression in sensitized human volunteers. Besides being the first detectable cytokine following an acute challenge, the predominant role of TNF was supported by the ability of anti-TNF antibody to abrogate the ear-swelling response in murine ACD reactions, both at the TNF mRNA level and relative to intensity of the inflammatory reactions. None of these inhibitory responses can be achieved equivalently by administration of antibodies for IL-2, IFN-.gamma., IL-3 or granulocyte/macrophage colony stimulating factor (GM-CSF). In a separate study, anti-TNF antibody demonstrated a dose-dependent suppression of the in vivo development of contact sensitivity. Since TNF appears to be the primary mediator of host responses, and can up-regulate IL-1 and IL-8 production both in an autocrine and paracrine fashion, it is logical and plausible that TNF plays the leading and central role in acute skin inflammation resulting from ACD.

8/7/18 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06658721 90331423 PMID: 2198387
Drugs in autoimmune diseases.
Herrmann D B; Bicker U
Boehringer Mannheim GmbH, Research and Development Division Therapeutics, FRG.
Klinische Wochenschrift (GERMANY, WEST) 1990, 68 Suppl 21 p15-25, ISSN 0023-2173 Journal Code: 2985205R
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Autoimmune diseases arise when autoimmunity or the loss of self tolerance results in tissue damages. Many mechanisms have been proposed for the origin of autoimmunity, including immunologic, viral, hormonal and genetic factors. All known parts of the immunological network are involved in causing immunopathologic symptoms. Therefore, more or less specific immunosuppressants are widely used in the treatment of autoimmune disorders which range from organ-specific, i.e. Hashimoto's thyroiditis, to non-organ-specific or systemic diseases, i.e. systemic lupus erythematosus. Unspecifically acting cytostatics do not only suppress autoimmune reactions but also create severe side-effects due to the impairment of immune responses against foreign antigens, leading, for example, to an increased risk of infections. Moreover, the genotoxic activity of cytostatics might induce malignancies. Corticosteroids are clinically well known and very active agents for the management of acute symptoms but different side-effects limit their use in the treatment of chronic diseases. Cyclosporin A has been an important step forward to a more specific prevention of organ transplant rejections and to the therapy of some autoimmune disorders. Modern approaches to immunosuppression include monoclonal antibodies directed against a variety of different determinants on immunocompetent cells. Ciamexone and Leflunomide which are in early clinical and preclinical development, respectively, might be interesting new drugs. Future immunopharmacologic drug research and development should lead to more specific, low molecular weight, orally active and chemically defined immunosuppressive compounds with good tolerability under long-term treatment of autoimmune diseases. (100 Refs.)
Record Date Created: 19900904

8/7/10 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE

03128576 EMBASE No: 1986196153
Methotrexate therapy in rheumatoid arthritis. Current status
Wilke W.S.; Mackenzie A.H.
Department of Rheumatic and Immunologic Disease, Cleveland Clinic Foundation, Cleveland, OH 44106 United States
Drugs (DRUGS) (Australia) 1986, 32/2 (103-113)
CODEN: DRUGA
DOCUMENT TYPE: Journal
LANGUAGE: ENGLISH

Antimetabolites which inhibit the enzyme dihydrofolate reductase, including aminopterin and methotrexate (amethopterin) have been used in

cancer and leukaemia chemotherapy since 1947. More recently, it has become a valuable alternative treatment for non-neoplastic diseases and has enjoyed its widest application in this respect as a treatment for severe psoriasis. In the subset of patients with psoriasis who develop erosive arthritis, early investigators observed improvement in both the skin and joint manifestations of psoriasis. Based largely on these observations, methotrexate has since been used to treat a variety of other arthritides and inflammatory/autoimmune diseases including Reiter's syndrome, polymyositis, polyarteritis nodosa, Wegener's granulomatosis, cyclitis, sarcoidosis and rheumatoid arthritis. In this article the authors discuss its use in rheumatoid arthritis.

03822941 EMBASE No: 1988272381
Reversal of recalcitrant cardiac allograft rejection with methotrexate
Costanzo-Nordin M.R.; Grusk B.B.; Silver M.A.; Sobotka P.A.; Winters G.L.
; O'Connell J.B.; Pifarre R.; Robinson J.A.
Section of Cardiology, Loyola University Medical Center, Maywood, IL
60153 United States
Circulation (CIRCULATION) (United States) 1988, 78/5 II SUPPL.
(III-47-III-57)
CODEN: CIRCA ISSN: 0009-7322
DOCUMENT TYPE: Journal
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Refractory cardiac transplant rejection is a major therapeutic dilemma. The effectiveness of methotrexate (MTX) in autoimmunue diseases prompted us to explore its efficacy in 10 cardiac transplant recipients, aged 20-53 years (39 +/- 13 years; mean +/- SD)m with biopsy evidence of drug-refractory cardiac allograft rejection. Nine cardiac transplant recipients were maintained on triple antirejection therapy (cyclosporine, azathioprine, and prednisone), and the remaining recipient was maintained on cyclosporine and prednisone. Rejection episodes treated with MTX occurred 20-422 days (165 +/- 137 days) after transplantation and were the sixth episode of rejection for one recipient, the third for four recipients, the second for four recipients, and the first for one recipient. Before MTX administration, cardiac allograft rejection persisted despite intensified immunosuppression including OKT3 antibody. MTX, given intravenously, orally, or by both routes at a dose of 10-175 mg (85 +/- 62 mg), reversed rejection in nine of 10 recipients (90%) within 7-63 days (26 +/- 18 days). Elevated pulmonary artery wedge pressures were reduced to normal levels after MTX therapy (15 +/- 3.5 before vs. 10.6 +/- 3.0 mm Hg after; $p < 0.05$). Leukopenia occurred in five cardiac transplant recipients after treatment with MTX. Adverse reactions to MTX resolved after MTX therapy was discontinued in all but one recipient. This recipient received one of the larger MTX doses (150 mg) and developed fatal Pseudomonas pneumonia. Twelve moderate rejection episodes recurred in nine recipients, seven episodes of which were successfully re-treated with MTX. Two of these seven recipients have now been rejection-free for 15 months. Of five recurrent episodes of cardiac transplant rejection not treated with MTX, two could not be reserved and were fatal. MTX may be a valuable drug for reversing refractory cardiac allograft rejection. Before MTX therapy gains wider use, however, a clearer understanding of its enhanced ability to suppress the bone marrow is needed.

8/7/9 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE

03376927 EMBASE No: 1987129504

Prolonged remission of insulin-dependent diabetes mellitus and thyroid autoimmunity following immunotherapy for acute lymphocytic leukemia
Hung W.; Maclaren N.K.
Department of Endocrinology and Metabolism, Children's Hospital National Medical Center, Washington, DC 20010 United States
American Journal of the Medical Sciences (AM. J. MED. SCI.) (United States) 1987, 293/4 (250-254)
CODEN: AJMSA
DOCUMENT TYPE: Journal
LANGUAGE: ENGLISH

A 6-year-old girl developed transient diabetes mellitus while receiving L-asparaginase, prednisone, vincristine, 6-mercaptopurine, and methotrexate as chemotherapy for acute lymphocytic leukemia that went into remission after 3 years of therapy. The patient subsequently developed autoimmune thyroid disease with hypothyroidism. Islet-cell antibodies were detected 1 year after anti-leukemic chemotherapy was stopped and 5 years before she developed overt insulin-dependent diabetes mellitus (IDDM). It is suggested that the immunosuppressive drugs received during anti-leukemic therapy may have delayed the appearance of IDDM and thyroid autoimmunity in a genetically susceptible patient.

8/7/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

07425084 BIOSIS NO.: 000091031073
METHOTREXATE AS AN ADJUNCT IN THE TREATMENT OF PERSISTENT MILD CARDIAC ALLOGRAFT REJECTION
AUTHOR: OLSEN S L; O'CONNELL J B; BRISTOW M R; RENLUND D G
AUTHOR ADDRESS: DIV. OF CARDIOL., UNIV. OF UTAH MED. CENT., 50 NORTH MEDICAL DR., SALT LAKE CITY, UTAH 84132.
JOURNAL: TRANSPLANTATION (BALTIMORE) 50 (5). 1990. 773-775. 1990
FULL JOURNAL NAME: TRANSPLANTATION (Baltimore)
CODEN: TRPLA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Because methotrexate arrests inflammation in autoimmune disease, we studied its efficacy in persistent low-grade cardiac allograft rejection. Seventeen patients aged 39.5 .+-. 0.9 years (mean .+-. SE) had persistent rejection despite previous therapy with high dose corticosteroids. Maintenance immunosuppression consisted of prednisone, azathioprine, and cyclosporine. The rejection episode treated with methotrexate occurred 180 .+-. 55.4 days posttransplantation. Patients had incurred 2.7 .+-. 0.3 previous episodes of rejection with the first episode occurring 30.6 .+-. 6.2 days post transplant. Methotrexate was administered orally in 3 doses to an average weekly dose of 12.8 .+-. 0.8 mg. The duration of methotrexate therapy was 9.0 .+-. 1.1 weeks. Sixteen of the seventeen persistent rejection episodes resolved by 22.8 .+-. 3.2 days of methotrexate therapy. Using methotrexate, the prednisone dose was decreased from 22.4 .+-. 4.8 mg/day at initiation of methotrexate to 9.7 .+-. 1.4 mg/day at the completion of methotrexate therapy ($P < 0.01$). Over a 306 .+-. 35-day follow-up, 9 of 17 patients (53%) have remained rejection-free. Leukopenia, necessitating reduction in azathioprine occurred in 10 patients. One patient developed herpes zoster during therapy. These data indicate that methotrexate is effective in resolving persistent cardiac allograft rejection with minimal morbidity. In addition, the use of methotrexate for treatment of rejection allows reduction in maintenance corticosteroid doses.

8/7/4 . (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

06929193 BIOSIS NO.: 000089062587
CYCLOSPORIN A FLUOCORTOLONE COMBINATION FOR TREATMENT OF AUTOIMMUNE DISEASES
AUTHOR: ARESU G; PASCALIS L; PIA G
AUTHOR ADDRESS: VIA ANCONA, 27 CAGLIARI.
JOURNAL: CLIN TER 131 (1). 1989. 3-21. 1989
FULL JOURNAL NAME: Clinica Terapeutica
CODEN: CLTEA
RECORD TYPE: Abstract
LANGUAGE: ITALIAN

ABSTRACT: The authors report the results obtained in treatment of various autoimmune diseases using cyclosporin A (CyA) in association with fluocortolone and/or methotrexate and cyclophosphamide. In all patients treated, complete long-lasting remission of the disease both from a clinical point of view and regarding laboratory tests was obtained. In some cases, this remission has lasted for several years since onset of therapy. The results obtained demonstrate the efficacy of CyA in treatment of autoimmune diseases and show that association with fluocortolone and/or methotrexate and cyclophosphamide by exploiting the combined action of these drugs, has enabled relatively low doses to be used. These however are still sufficient to induce satisfactory immunosuppression and avoid side effects. In this context, the importance of monitoring drug blood levels is underlined, also in view of the fact that each patient has a different capacity for intestinal CyA absorption.

8/7/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

06720784 BIOSIS NO.: 000088030210
ANTIPROLIFERATIVE EFFECTS OF METHOTREXATE ON PERIPHERAL BLOOD MONONUCLEAR CELLS
AUTHOR: OLSEN N J; MURRAY L M
AUTHOR ADDRESS: B-3219 MCN, VANDERBILT UNIV., NASHVILLE, TENN. 37232.
JOURNAL: ARTHRITIS RHEUM 32 (4). 1989. 378-385. 1989
FULL JOURNAL NAME: Arthritis and Rheumatism
CODEN: ARHEA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Methotrexate was added to cultured mononuclear cells from the peripheral blood of normal individuals and patients with rheumatoid arthritis (RA) to study the drug's effects on mononuclear cell proliferation and antibody synthesis. In the presence of methotrexate, marked antiproliferative effects (to levels < 15% of baseline) were seen with 3H-deoxyuridine, but not with 3H-thymidine, as the marker of cell division. This difference was not due to altered kinetics of proliferation or the presence of salvage nucleotides in the culture medium. The absence of suppression of antibody production preactivated by pokeweed mitogen in vitro and the low levels of suppression of spontaneous IgM rheumatoid factor production by blood mononuclear cells from RA patients suggested a relative resistance of activated cells to the effects of methotrexate. The effects of methotrexate on both cell proliferation and antibody synthesis were completely reversed by the addition of high concentrations of exogenous folinic acid. The results suggest that methotrexate has effects on immunocompetent cells that may contribute to the efficacy of this drug in the treatment of RA

and other autoimmune diseases.

8/7/6 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

05009791 BIOSIS NO.: 000031084923
20 YEARS OF METHOTREXATE IN THE TREATMENT OF AUTOIMMUNE DISEASES
AUTHOR: MIESCHER P A
AUTHOR ADDRESS: DEP. MED., DIV. D'HEMATOL., HOP. CANTONAL UNIV. GENEVE, 25 RUE MICHELI-DU-CREST, CH-1211 GENEVE 4, SWITZERLAND.
JOURNAL: RAU, R. (ED.). RHEUMATOLOGY, VOL. 9. LOW-DOSE METHOTREXATE THERAPY IN RHEUMATIC DISEASES; SYMPOSIUM, DUESSELDORF, WEST GERMANY, SEPT. 28-30, 1984. XI+268P. S. KARGER AG: BASEL, SWITZERLAND; NEW YORK, N.Y., USA.
ILLUS. ISBN 3-8055-4236-4. 0 (0). 1986. 46-50. 1986
CODEN: RHEUB
RECORD TYPE: Citation
LANGUAGE: ENGLISH

8/7/7 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

03911605 EMBASE No: 1989080598
Chronic liver diseases: Current therapeutic options
Kaplan M.M.
Tufts University School of Medicine, Boston, MA United States
Hospital Practice (HOSP. PRACT.) (United States) 1989, 24/3 (111-130)
CODEN: HOPRB ISSN: 8750-2836
DOCUMENT TYPE: Journal
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Five years ago there was little worth saying on the subject. Now we can state: Autoimmune chronic hepatitis can be effectively treated; chronic hepatitis B responds to alpha-interferon, as does chronic non-A, non-B hepatitis; colchicine is beneficial in primary biliary cirrhosis; and methotrexate seems even more promising in both that disease and primary sclerosing cholangitis.

8/7/8 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

03822941 EMBASE No: 1988272381
Reversal of recalcitrant cardiac allograft rejection with methotrexate
Costanzo-Nordin M.R.; Grusk B.B.; Silver M.A.; Sobotka P.A.; Winters G.L.; O'Connell J.B.; Pifarre R.; Robinson J.A.
Section of Cardiology, Loyola University Medical Center, Maywood, IL 60153 United States
Circulation (CIRCULATION) (United States) 1988, 78/5 II SUPPL. (III-47-III-57)
CODEN: CIRCA ISSN: 0009-7322
DOCUMENT TYPE: Journal
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Refractory cardiac transplant rejection is a major therapeutic dilemma. The effectiveness of methotrexate (MTX) in autoimmunue diseases prompted us to explore its efficacy in 10 cardiac transplant recipients, aged 20-53 years (39 +/- 13 years; mean +/- SD)m with biopsy evidence of drug-refractory cardiac allograft rejection. Nine cardiac

transplant recipients were maintained on triple antirejection therapy (cyclosporine, azathioprine, and prednisone), and the remaining recipient was maintained on cyclosporine and prednisone. Rejection episodes treated with MTX occurred 20-422 days (165 +/- 137 days) after transplantation and were the sixth episode of rejection for one recipient, the third for four recipients, the second for four recipients, and the first for one recipient. Before MTX administration, cardiac allograft rejection persisted despite intensified immunosuppression including OKT3 antibody. MTX, given intravenously, orally, or by both routes at a dose of 10-175 mg (85 +/- 62 mg), reversed rejection in nine of 10 recipients (90%) within 7-63 days (26 +/- 18 days). Elevated pulmonary artery wedge pressures were reduced to normal levels after MTX therapy (15 +/- 3.5 before vs. 10.6 +/- 3.0 mm Hg after; $p < 0.05$). Leukopenia occurred in five cardiac transplant recipients after treatment with MTX. Adverse reactions to MTX resolved after MTX therapy was discontinued in all but one recipient. This recipient received one of the larger MTX doses (150 mg) and developed fatal Pseudomonas pneumonia. Twelve moderate rejection episodes recurred in nine recipients, seven episodes of which were successfully re-treated with MTX. Two of these seven recipients have now been rejection-free for 15 months. Of five recurrent episodes of cardiac transplant rejection not treated with MTX, two could not be reserved and were fatal. MTX may be a valuable drug for reversing refractory cardiac allograft rejection. Before MTX therapy gains wider use, however, a clearer understanding of its enhanced ability to suppress the bone marrow is needed.

08291281 BIOSIS NO.: 000094062579
PHASE I-II TRIAL OF A MONOCLONAL ANTI-TUMOR NECROSIS FACTOR ALPHA ANTIBODY FOR THE TREATMENT OF REFRACTORY SEVERE ACUTE GRAFT-VERSUS-HOST DISEASE
AUTHOR: HERVE P; FLESCH M; TIBERGHIEN P; WIJDENES J; RACADOT E; BORDIGONI P ; PLOUVIER E; STEPHAN J L; BOURDEAU H; HOLLLER E; ET AL
AUTHOR ADDRESS: CENTRE REGIONAL DE TRANSFUSION SANGUINE, 1 BD FLEMING, 25000 BESANCON, FRANCE.
JOURNAL: BLOOD 79 (12). 1992. 3362-3368. 1992
FULL JOURNAL NAME: Blood
CODEN: BLOOA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: In a multicenter pilot study, 19 patients with severe acute graft-versus-host disease (aVBHD) refractory to conventional therapy and serotherapy with a monoclonal anti-interleukin-2 receptor antibody were treated by in vivo infusions of a monoclonal anti-tumor necrosis factor .alpha. (TNF.alpha.) antibody (B-C7). Ten patients were grafted from a genotypically identical sibling, five from an HLA-mismatched family member, and four from an HLA-matched unrelated donor. Before B-C7 treatment, 15 patients had grade IV and four had grade III GVHD. In all cases, patients received cyclosporine/ methotrexate as aGVHD prophylaxis. Patients were administered increasing doses of antibody (from 0.1 to 0.4 mg/kg). The antibody was infused in bolus daily for 4 days and then every other day twice (6 doses). No side effects were observed during treatment regardless of the dose level used. Changes in peripheral blood cell counts occurred in 8 of the 19 patients and appeared to be unrelated to B-C7. No truly complete response was observed; eight patients achieved a very good partial response (42.6%) and six a partial response (31.5%). The treatment was ineffective in five patients (26.4%). When present, the response occurred early (< 3 days). In the 14 responding patients, gut lesions responded best (100%), followed by skin (85%) and liver (35.7%) lesions. In 9 of 11 evaluable patients (81%), GVHD recurred when treatment was discontinued in a median delay of 3 days (range, 2 to 120 days). All except one died from aGVHD. Two patients did not experience GVHD

recurrence and are still alive 13 and 18 months post-bone marrow transplantation. This pilot study shows that a monoclonal anti-TNF .alpha. antibody may be of benefit to some patients with severe refractory aGVHD, but is ineffective to prevent GVHD recurrence in the majority of cases.

12/7/2 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

05215370 EMBASE No: 1992355604
Use of monoclonal antibodies in vivo as a therapeutic strategy for alloimmune or autoimmune reactivity: The Besancon experience
Herve P.; Racadot E.; Wendling D.; Rumbach L.; Tiberghien P.; Cahn J.Y.; Flesch M.; Wijdenes J.
Centre Reg. de Transfusion Sanguine, 1 Boulevard Fleming,25020 Besancon France
Immunological Reviews (IMMUNOL. REV.) (Denmark) 1992, -/129 (31-55)
CODEN: IMRED ISSN: 0105-2896
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH

---------- 12/7/12 (Item 11 from file: 73)
DIALOG(R)File 73:EMBASE

04302723 EMBASE No: 1990185279
Serum tumor necrosis factor-alpha levels in allogeneic bone marrow transplant recipients with acute leukemia
Hirokawa M.; Takatsu H.; Niitsu H.; Nishinari T.; Nimura T.; Itoh T.; Chubachi A.; Miura I.; Yoshida K.; Endo Y.; Miura A.B.
The Third Department of Internal Medicine, Akita University School of Medicine, Akita 010 Japan
Tohoku Journal of Experimental Medicine (TOHOKU J. EXP. MED.) (Japan) 1989, 159/3 (237-244)
CODEN: TJEMA ISSN: 0040-8727
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

We determined the serum levels of tumor necrosis factor-alpha (TNF) in allogeneic bone marrow transplant recipients in order to evaluate the relationship between TNF and graft-versus-host disease (GVHD). Eight patients with acute leukemia receiving an HLA-identical marrow graft were studied. Samples from healthy subjects and pretransplant recipients were all negative for TNF. Six of eight patients had detectable levels of TNF in serum after transplantation. All three patients with acute GVHD, and three of five patients without acute GVHD had elevated TNF levels in serum. Among the patients with increased TNF levels, documented infection was demonstrated in only one patient, with a clinical diagnosis of B19 parvovirus infection. Serum TNF levels were elevated when the WBC counts were more than 2,000/mul. However, serum concentrations of TNF significantly correlated with body temperature. Although we could not conclude definitely that serum TNF levels correlated with severity of GVHD, it was suggested that TNF may be produced as a result of latent infections or immunological reaction against non-HLA allogeneic antigens.

12/7/11 (Item 10 from file: 73)
DIALOG(R)File 73:EMBASE

04822973 EMBASE No: 1991317709
Soluble CD8, IL-2 receptor, and tumor necrosis factor-alpha levels in steroid-resistant acute graft-versus-host disease: Relation with subsequent response to anti-IL-2 receptor monoclonal antibody treatment
Tiberghien P.; Racadot E.; Lioure B.; Delain M.; Girard A.; Wijdenes J.; Plouvier E.; Flesch M.; Cahn J.-Y.; Herve P.
Service d'Hematologie, C.H.U. J. Minjoz, Bvd. Fleming,25000 Besancon France
Transplantation (TRANSPLANTATION) (United States) 1991, 52/3 (475-480)
CODEN: TRPLA ISSN: 0041-1337
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Serial determination of soluble CD8 (sCD8), soluble IL-2 receptors (sIL-2R), and tumor necrosis factor-alpha serum levels were performed in bone marrow transplant patients upon initiation, day 0 (D0) and at D10 of an anti-IL-2 receptor (alpha chain) monoclonal antibody (B-B10) in vivo treatment for steroid-resistant grade >=2 acute graft -versus-host disease (aGVHD). D0 and D10 sCD8 serum levels correlated strongly with response to B-B10 treatment (p=.003 and .001, respectively); 76% of the patients with D0 sCD8 levels <500 U/ml responded favorably to B-B10 treatment, versus only a 30% response if the sCD8 levels were >500 U/ml (p=.02). Likewise, D0 tumor necrosis factor-alpha levels significantly correlated with subsequent response to B-B10 treatment (p=.03). D0 sIL-2R levels were not significantly different in B-B10-responsive and nonresponsive aGVHD patients. These results suggest that the serial determination of sCD8 and TNF serum levels could provide valuable predictive information as to steroid-resistant aGVHD responsiveness to anti-IL-2R treatment.

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24/7/1 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

04622479 EMBASE No: 1991116522
Granulocytic sarcoma of the ileum treated by bone marrow transplantation
Kowal-Vern A.; Johnson F.L.; Trujillo Y.; Nachman J.; Radhakrishnan J.; Conard P.; Gaynon P.
Department of Pediatrics, Loyola University Medical Center, 2160 South First Avenue, Maywood, IL 60153 United States
American Journal of Pediatric Hematology/Oncology (AM. J. PEDIATR. HEMATOL. ONCOL.) (United States) 1991, 13/1 (34-38)
CODEN: APHOD ISSN: 0192-8562
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

An 8-year-old boy with a granulocytic sarcoma of the proximal ileum metastatic to mesenteric lymph nodes was placed into complete remission with surgical excision of the primary tumor and conventional induction chemotherapy with daunorubicin and cytosine arabinoside. He was then treated with high dose cytosine arabinoside, fractionated total body irradiation, and allogeneic marrow transplantation from his 22-month-old brother who was completely matched at the major histocompatibility complex. Methotrexate was given following the transplant to prevent graft-versus-host disease (GVHD). His post-transplantation course was complicated by a transient autoimmune hemolytic anemia related to an ABO blood group incompatibility and hepatic fungal microabscesses which responded to Amphotericin therapy. Four years following the transplant the patient remains in complete remission. The prognosis for patients with granulocytic sarcoma has been poor although,

perhaps, improved over the past decade. This is the first published case report of successful treatment of a granulocytic sarcoma of the ileum by allogeneic marrow transplantation.

24/7/2 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

03572911 EMBASE No: 1988022347
High levels of anti-cytoskeleton autoantibodies are frequently associated with chronic GVHD
Dighiero G.; Intrator L.; Cordonnier C.; Tortevoye P.; Vernant J.-P.
Unite d'Immunohematologie et d'Immunopathologie, Institut Pasteur, 75724 Paris Cedex 15 France
British Journal of Haematology (BR. J. HAEMATOL.) (United Kingdom)
1987, 67/3 (301-305)
CODEN: BJHEA ISSN: 0007-1048
DOCUMENT TYPE: Journal
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Twenty-two patients (acute myeloid leukaemia 13, acute lymphoid leukaemia 5, chronic myeloid leukaemia 4) with an average age of 25 years (range 8-36 years), had received allogeneic bone marrow transplantation (BMT) form an HLA identical sibling. The BMT recipients were followed up for a period of 4-65 months. All patients were given cyclophosphamide, total body irradiation and methotrexate in order to prevent graft-versus-host disease (GvHD). Eleven of 22 patients exhibited chronic graft versus host disease (cGvHD) (extensive in five, limited in six at the time of the study) assessed by clinical and histological parameters. Serum samples were collected from these patients, before BMT (except in one case) and then every 2 to 3 months. Sequential studies to determine the presence of autoantibodies against cytoskeletal proteins (actin, tubulin, myosin), dsDNA and dDNA in these sera were performed by an ELISA method. Simultaneously, immunoelectrophoresis and measurement of complement fractions C3, C4 were performed on each sample. High levels of autoantibodies against cytoskeletal proteins were found in 10/11 patients with cGvHD and were absent in 11/11 patients without cGvHD: none of them exhibited anti-DNA activity. At the same time, C4 levels were decreased in seven of these patients with cGvHD. Monoclonal immunoglobulins IgG and IgM (2-15 g/l) were found in 8/11, but the antibody activity was never found to be located within the M component. These results show a direct relationship between the presence of these autoantibodies and occurrence of cGvHD and indicate that they may constitute an immunological marker related to this complication. However, their predictive value is not clearly evident in this retrospective series as in some patients they preceded clinical signs of cGvHD, whereas in others they were associated with the onset of cGvHD.

24/7/3 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06081539 89156447 PMID: 2784139
Immunomodulation by low-dose methotrexate. I. Methotrexate selectively inhibits Lyt-2+ cells in murine acute graft-versus-host reactions.
Gibbons J J; Lucas J
Department of Inflammation and Immunology, American Cyanamid Company, Pearl River, NY 10965.
Journal of immunology (Baltimore, Md. : 1950) (UNITED STATES) Mar 15 1989, 142 (6) p1867-73, ISSN 0022-1767 Journal Code: 2985117R
Document type: Journal Article
Languages: ENGLISH

Main Citation Owner: NLM
Record type: Completed
We have studied the effect of methotrexate in murine acute graft vs host (GvH) disease at concentrations analogous to those used in human rheumatoid arthritis. The GvH reaction was induced by i.v. injection of parental spleen cells into a normal F1 recipient. The acute suppression of T cell function in GvH mice was prevented by methotrexate given orally for 10 days at 1.0 or 0.5 mg/kg but not at 0.25 mg/kg. T cell mitogen response and IL-2 secretion that were inhibited in GvH mice were restored by methotrexate. Protection from immunosuppression in drug-treated GvH mice lasted at least 3 wk after drug dosing was stopped. The mechanism of the protective effect appears to be a preferential inhibition of donor and host Lyt-2+ Ts cell proliferation. In mixing experiments we found that methotrexate inhibited Ts function in GvH mice. By dual fluorescence labeling we showed that the engraftment of donor Lyt-2+ cells was prevented by drug treatment. This was not true of donor L3T4+ cells which were clearly present in the spleens of GvH mice after methotrexate treatment. These donor L3T4 cells were functional in that they induced the production of anti-DNA autoantibodies in the methotrexate-treated GvH mice.
Record Date Created: 19890417

24/7/4 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05744671 88159725 PMID: 3279575
Immunohematologic consequences of major ABO-mismatched bone marrow transplantation.
Sniecinski I J; Oien L; Petz L D; Blume K G
Blood Transfusion Services, City of Hope National Medical Center, Duarte, CA 91010.
Transplantation (UNITED STATES) Mar 1988, 45 (3) p530-4, ISSN 0041-1337 Journal Code: 0132144
Contract/Grant No.: CA 30206; CA; NCI; CA 33572; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Twelve of 58 (21%) evaluable patients of blood group 0 who received a bone marrow transplant (BMT) from an HLA-matched sibling of a donor of group A or B developed significant immunohematologic problems in the posttransplant period. Anti-A or anti-B isohemagglutinins persisted for longer than 120 days post-BMT in nine patients and are still present in three patients at days +162 to +605. Red cell production as indicated by a reticulocyte count of greater than 0.5% was delayed to 40 days or more in nine patients, and in five of these was markedly delayed to 170 days or longer. One patient does not as yet have red cell production on day +605 in spite of having had 13 plasma exchanges performed to reduce the anti-B titer. Five patients experienced overt hemolysis, manifested by a sudden drop in hemoglobin of 1.5 to 4 gm/dl (median = 2.5 mg/dl), starting on day +37 to +105 (median = +65), persisting for 10 to 94 days (median = 36 days). Hemolysis and a delay in the onset of erythropoiesis beyond 170 days were more frequent in 30 patients treated with cyclosporine/prednisone than in 28 patients treated with methotrexate/prednisone for graft-versus-host disease prophylaxis. Our data indicate that ABO major mismatched BMT can be associated with significant immunohematologic consequences, some of which occur more frequently in association with cyclosporine administration.
Record Date Created: 19880411